

### **Remarks**

Claims 1-21, 31, 35-38, 40-45, 47 and 49 were pending in this application. Claims 1-6, 8, 10-11, 31, 36 and 49 have been amended, and new claim 75 added. Hence claims 1-21, 31, 35-38, 40-45, 47, 49 and 75 are pending.

#### *Interview Summary*

Applicants gratefully acknowledge the courtesy of a personal interview granted to applicant's representatives by Examiners Counts and Le on November 29, 2006. A draft version of a Second Declaration of Robert Buck was discussed at that meeting, as was the Boehringer et al. reference. Applicant emphasized that the Boehringer et al. reference repeatedly emphasizes *non-bibulous* flow in which all of the dispersed components (including the analyte and tracer) are carried at substantially equal rates, and that this non-bibulous flow would by definition avoid separation of the analyte and tracer as claimed by applicant. The Second Declaration of Buck provided evidence that the differential flow provided by applicant's claimed test strip is capable of providing a greater difference in signal between the primary and secondary capture zones when analyte is present. In addition, the declaration demonstrates that delayed release of conjugate from the mobilization zone helps avoid a bolus of tracer from reaching the primary capture zone and leaking past it.

The Examiners also requested that the obviousness type double patenting rejection be addressed in applicant's written response.

Applicant noted that it was unclear whether the rejection being asserted in view of Boehringer et al. was an inherent anticipation rejection under Section 102 or an obviousness rejection under Section 103. The Examiners asked applicant to address both possibilities.

#### *Section 112 Rejection*

Claim 1 was said to lack antecedent basis for "an analog." That term has been removed from claim 1 and the rejection overcome.

#### *Inherency under Section 102/103*

Claims 1-5, 10-13, 20, 21, 31, 35-36, 40-41, 45 and 49 were rejected as being obvious in view of Boehringer et al. (WO 98/39657). Boehringer was said to disclose a test strip made of materials similar to those in applicant's specification, such that separation of the tracer and analyte would occur before they reached the primary capture zone. The Office action appears to

acknowledge that Boehringer does not refer to such differential flow, and therefore contends that the separation would only inherently occur.

As applicants demonstrated in detail in their May 5, 2006 response (and noted during the November 29, 2006 interview), Boehringer et al. can not be said to inherently achieve separation of the tracer and analyte before they reach the primary capture zone. Many different factors interact to achieve the desired separation. As noted in applicant's specification, these factors include the size, polarity and charge of the tracer, as well as a matching of the pore size to the size of the conjugate (page 21, lines 1-22, especially lines 19-22), the position of the conjugate on the test strip (page 24, lines 11-14 and 22-24), placing the conjugate on the test strip in the presence of delayed release immobilization agent (such the sucrose, mannitol, glycerol, PVA or PVP discussed at page 24, lines 26-31), or placing the mobilization zone on the test strip under a sample application pad (pages 17-18 and FIG. 2). As noted particularly at page 21, lines 19-22, the combinations of such factors is empirically determined to achieve differential flow in which the analyte reaches the primary capture zone ahead of the tracer. Separating the tracer and analyte before they reach the primary capture zone is not something that is achieved by accident or happenstance, but is instead the result of the deliberate selection of variables as outlined in applicant's specification.

Applicants have even submitted (with their May 17, 2005 response) the First Declaration of Buck dated May 15, 2005 that succinctly demonstrated that varying even one simple parameter can eliminate the separation of the tracer and analyte before they reach the primary capture zone. Dr. Buck applied a urine sample that contained a morphine analyte to a bibulous nitrocellulose substrate on which colored latex tracer particles were present in a mobilization zone. As the liquid and analyte migrated through the mobilization zone, the latex tracer particles did not immediately separate from the liquid that carried the analyte. When the mobilization zone was only 4 mm from the primary capture zone, the colored latex tracer front reached the primary capture zone simultaneously with the analyte. However when the mobilization zone was farther away from the primary capture zone (13 mm and 20 mm) the colored latex tracer front was seen to lag behind the liquid analyte front so that the analyte reached the primary capture zone before the latex tracer. In addition, the tracer signal from the primary capture zone was not reduced when the mobilization zone was only 4 mm from the primary capture zone but it was reduced when the mobilization zone was moved farther away. This reduction of signal at greater

distances indicated that the separation of the tracer from the analyte allowed the analyte to reach the primary capture zone and bind to it before the tracer, so that more of the tracer was available for binding to downstream capture zones.

The May 15, 2005 Declaration of Buck was said to be unconvincing because the data in it was not commensurate in scope with applicants' claims. However, as discussed during the November 29 interview, that objection mistakenly assumed that the Declaration was being submitted as evidence of unexpectedly superior results. The Declaration had instead been submitted as evidence that Boehringer et al. did not *inherently anticipate* the pending claims. According to MPEP 2112, inherent disclosure by a reference requires that a certain result or characteristic must *necessarily* be present, and that it may not be established by *probabilities* or *possibilities*. The Examiner has already acknowledged (in the October 18, 2005 advisory action) that applicants have shown that "it is quite possible for the detectable tracer and analyte to reach the primary capture zone together for example if the detectable tracer does not migrate a distance sufficient for the separation of the wave fronts to occur." Hence the PTO has acknowledged that Boehringer et al. does not inherently disclose applicant's claimed invention, because the separation of the tracer and analyte is not necessarily present in the cited reference.

Applicants also noted during the November 29 interview that Boehringer et al. does not disclose any embodiment of a lateral flow assay in which separation of the analyte and tracer could occur. Although the reference states in passing that the support matrix may be capable of bibulous or non-bibulous flow (page 31, lines 15-16), every example in the cited reference is one in which the substrate is rendered non-bibulous, for example by treating it with a blocking agent such as BSA or methylated-BSA (page 32, lines 23-28). See, for example, page 24, lines 27-28; page 31, lines 26-27; and page 38, lines 1-10 and 13-16. Note particularly the description at pages 52-54 of how the flow devices were constructed. In every instance the sample receiving and disseminating (mobilization) zones are said to be constructed from Sontara using the procedure earlier described in association with FIG. 1 (which was described on page 38 as being rendered non-bibulous by saturating with methylated BSA). The description of the capture zone membrane on page 53 also refers back to the earlier description of FIG. 1, in which nitrocellulose was blocked with a BSA blocking buffer. All of the examples disclosed in Boehringer et al. use a non-bibulous substrate in which "all of the dissolved or dispersed components of the liquid are carried at substantially equal rates and with relatively unimpaired flow, laterally through the

membrane or matrix, as opposed to preferential retention of one or more components as would occur, e.g., in materials capable of adsorbing or imbibing one or more components” (page 31, lines 17-21). This is the opposite of the bibulous, differential flow required by applicant’s claims.

It is indisputable that the Boehringer et al. reference fails to disclose the claimed test strip in which a “bibulous substrate selectively delays migration of the detectable tracer so that the analyte migrates ahead of the detectable tracer and distal flow of analyte reaches the primary capture area before” the detectable tracer. There is no inherent anticipation.

### *Obviousness Rejection*

Although there is no inherent anticipation of the claims, the Office action alleges that the claimed invention is obvious over Boehringer et al. because that reference discloses attaching an analyte analog to BSA coated latex microspheres that flow with a sample through a substrate that has a pore size of 1000 to 200000 nm. While the Office action admits that the cited reference is silent about the analyte reaching the primary capture area before the tracer, the claimed invention is said to nonetheless be obvious because “one of ordinary skill in the art would recognize that the rate of migration for the labeled analyte analog would be slower than the rate of migration of the analyte and thus the analyte would reach the primary capture area before the detectable tracer.” Since applicants have already demonstrated that this statement is not true, the basis for the obviousness rejection is unfounded and the rejection must be withdrawn. It is only possible to achieve differential migration by choosing among variables with the intention of achieving the claimed differential migration. Factors such as the size of the tracer relative to the size of the pore, the distance from the mobilization zone to the capture zone, and the use of bibulous flow are appropriately combined to arrive at the claimed separation of the tracer, and there is no teaching in Boehringer et al. for selecting such a combination of factors. A prima facie case of obviousness has not been established.

As stated in MPEP 2141.02, “Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).” Since Boehringer et al. neither discloses nor suggests delaying migration of the tracer relative to the analyte, it can not be said to establish a prima facie case for selecting a particular combination of features that would achieve

differential flow. The reference does not even mention the desirability of achieving differential flow, so it can not be said to suggest the selection of the various combinations of variables that would achieve it. Moreover, Boehringer et al. incorporates by reference a number of prior patents and patent applications that teach the importance of non-bibulous flow. See discussion at pages 10-11 of applicant's amendment submitted May 5, 2006. These incorporated references explicitly teach away from the bibulous flow claimed by applicants.

Even if a prima facie case of obviousness had been established (which it has not), that prima facie case would be rebutted by the Second Declaration of Robert Buck. This Declaration shows that delaying the migration of the detectable tracer relative to the analyte provides an unexpectedly superior result. The migration of the analyte ahead of the tracer allows the analyte time to bind with and occupy the binding sites in the primary capture area, thereby reducing binding of the tracer to the primary capture area so that more of the tracer binds at the secondary capture area. Greater binding at the secondary capture area produces a greater difference in the signal between the primary and secondary capture areas when analyte is present.

#### *Specific Claims*

Claim 1 has been amended to state that the bibulous substrate selectively delays migration of the detectable tracer so that that the analyte migrates ahead of the detectable tracer and a distal flow of analyte reaches the primary capture area before a distal flow of detectable tracer. As already noted, Boehringer does not contain any example of a lateral flow test strip that inherently anticipates the claimed invention. All of the specific examples employ non-bibulous flow in which the tracer and analyte are carried at equal rates. Moreover, Boehringer et al. does not disclose or suggest a substrate that selectively delays migration of the tracer as claimed. Although the cited reference notes that some variables can be varied (such as whether the substrate is bibulous, selection of pore sizes of 1 to 250 microns (page 31, line 31), and selection of a variety of tracers (such as latex, colloids, latex, erythrocytes and other listed on page 34) there is no teaching in the reference that these variables (and others such as the distance between the mobilization and primary capture area) are chosen in such a way that bibulous substrate delays the migration of the tracer relative to the analyte. The first Declaration of Buck demonstrated that varying even simple factors such as the distance between the mobilization and primary capture area can eliminate differential flow. The cited reference neither discloses the

desired end result (differential flow) nor states how it would be achieved. A prima facie case of obviousness has not been established with respect to claim 1.

Moreover, as demonstrated by the Second Declaration of Buck, the claimed delay in migration of the tracer provides a greater binding of conjugate to the primary capture area in the absence of analyte, and a much lesser binding of conjugate to the primary capture area in the presence of analyte. See particularly the summary of the results in paragraph 8 of the Second Declaration of Buck. Hence even if a prima facie case of obviousness had been established, it would be rebutted by this demonstration of unexpected results with the claimed delayed migration of the tracer.

### *Claim 2*

Claim 2 states that the detectable tracer is present on the test strip in a position that selectively delays migration of the detectable tracer through the bibulous substrate so that the detectable tracer reaches the primary capture area after the analyte. The Office action alleges that one of skill in the art would recognize that the rate of migration of the tracer would be slower than the rate of migration of the analyte. As already noted, that is not the case because achieving the claimed migration involves selection of a variety of interacting variables. Boehringer et al. does not even recognize the significance of differential migration; it could hardly be said to suggest the judicious selection of variables to achieve the claimed delayed migration of the tracer and produce the superior results described in the Second Declaration of Buck.

In addition, there is no disclosure or suggestion in the prior art that the detectable tracer be present *in a position* that delays migration of the tracer so that the tracer reaches the primary capture area after analyte reaches the primary capture area. As already acknowledged by the advisory action, there is no inherent anticipation of the claim by Boehringer et al. The Office action apparently alleges that the claims invention is obvious because one skilled in the art would recognize that the position could be varied in this manner to achieve the delayed migration of the tracer. However there is nothing in the reference that supports that allegation. The mere possibility that pore size, placement of the tracer, tracer size and a variety of other factors could be arranged to achieve differential flow does not establish a prima facie case of obviousness. Since the advisory action has acknowledged that there is no inherent anticipation, the PTO would

have to rely on some specific disclosure in the reference on which to base an obviousness rejection. The possibility that someone could select a combination of variables that would yield the claimed differential flow does not support a prima face case of obviousness.

### *Claim 3*

Claim 3 has been amended to state that the detectable tracer is a delayed release detectable tracer that migrates through the test strip behind the analyte as the liquid sample migrates through the test strip. Delayed release tracers are supported, for example, in applicant's specification at page 24, lines 25-31. Boehringer et al. is silent about providing a delayed release tracer because that reference does not disclose, suggest or appreciate the advantages of delaying release of the tracer. Moreover, the Second Declaration of Buck demonstrates that delaying release of the tracer avoids "leak through" of tracer to the secondary capture area in the absence of analyte, and helps reduce the amount of tracer that binds to the primary capture area in the presence of analyte. The delayed release tracer is not disclosed or suggested by the prior art, and in any event provides unexpectedly superior results.

Boehringer et al. does not disclose any lateral flow test strip in which the tracer is a delayed release tracer. All examples in that cited reference disclose that the labeling zone pad 16 was rendered non-bibulous (page 38, lines 13-16) by providing a Sontara® pad that has been saturated in methylated BSA. This labeling pad 14 is shown in the figures as being mounted on a flow matrix 16. Although Boehringer et al. states that the "support matrix of the device may be capable of either bibulous or non-bibulous lateral flow" (page 31, lines 15-16) the reference never teaches that the labeling pad itself can be bibulous. Since the labeling pad (that contains the tracer) is in all instances nonbibulous, it by definition does not delay release of the tracer. Nonbibulous flow in Boehringer et al. is said to require that all of the dissolved components are carried at substantially equal rates, which is the antithesis of the delayed release tracer of claim 4. Since the cited reference is devoid of any disclosure or suggestion of a delayed release tracer of claim 4, a prima facie case of obviousness has not been established and the claim is allowable.

### *Claims 4, 36 and 49*

Claim 4 states that the mobilization zone is a bibulous substrate. This amendment is supported, for example, at page 16, lines 10-11 (the mobilization zone is located on the

collection member 22) and page 15, lines 29-30 (the collection member is bibulous). As noted in the discussion of claim 3 above, there is no disclosure in Boehringer et al. that the labeling zone is bibulous; it is instead specifically rendered non-bibulous. In the absence of a disclosure that the labeling zone is bibulous, there is no prima facie case of obviousness with respect to claim 4. At most, Boehringer states that the *support matrix* could be bibulous, but Boehringer's labeling pad (that is placed on the support matrix) is always non-bibulous.

The cited reference certainly did not appreciate that providing a bibulous mobilization zone would allow the tracer and analyte to begin to separate in the labeling zone to promote the beneficial results discussed in the Second Declaration of Buck. The unexpectedly superior results achieved by the bibulous mobilization zone would rebut any prima facie case of obviousness, if one had been established.

Claims 36 and 49 have also been amended to state that the mobilization zone is bibulous, unlike the mobilization zone in Boehringer et al. which has been treated with a blocking agent to render it non-bibulous.

#### *Claim 5*

Claim 5 calls for the detectable tracer to be larger than the analyte but sufficiently smaller than pores of the porous strip to allow the tracer to migrate through the bibulous strip more slowly than the analyte migrates along the path of liquid flow. This amendment is supported at page 21, lines 13-22. The Boehringer reference does not disclose such a relationship, because the only type of flow actually performed in that reference is a non-bibulous flow in which the analyte and tracer migrate together along with surface of the test strip without separating from one another. Although the cited reference offhandedly states that the support matrix can be bibulous, and a broad range of pore sizes are mentioned, there is no discussion or enablement of choosing a pore size that is appropriate to permit slowed migration of the tracer through the porous substrate without stopping migration of the tracer altogether. A mere statement in Boehringer et al. that bibulous flow might be achieved is not a specific disclosure of the claimed relationship between the size of the pores and the tracer. Similarly, the mere recitation of pore sizes in the cited references falls well short of establishing a prima facie case of obviousness with respect to the particularly claimed relationship.



### *Claim 6*

Claim 6 states that the detectable tracer is an analyte analog positioned in the mobilization zone beneath the surface of the test strip along which the liquid sample migrates through the test strip to the primary capture area. The Office action contends that it would be obvious to place the mobilization zone in this position, as shown in Fredrickson, because that reference allegedly teaches that this placement of the tracer “provides for a rapid, volume, timing and temperature independent visually read test strip.” Applicants have reviewed Fredrickson and found no such teaching that placing the tracer in this position achieves any of those advantages. Although Fredrickson states that these goals are an object of his overall invention (column 2, lines 44-47), there is no teaching that placement of the tracer beneath the surface of the test strip achieves those goals. In addition, claim 6 has been amended to state that the tracer comprises an analyte analog, while Fredrickson only shows a tracer that is a “labeled binding partner for the analyte of interest” such as an antibody (column 3, lines 45-48).

A prima facie case of obviousness has not been established with respect to claim 6. Even if Fredrickson were combined with Boehringer et al. as proposed by the Office action, the result would be a labeled antibody, and not the labeled analyte analog of claim 6. Hence even if the proposed combination were made the claimed invention would not result.

In addition, the Office action does not establish a motivation in the art for making the proposed combination. Contrary to the allegation in the Office action, there is nothing in the Fredrickson reference that ties its overall object (a rapid visually read test strip that is timing and temperature independent) to a detectable tracer beneath the surface of the test strip. Hence the Office action does not identify an actual motivation in the cited prior art for making the proposed combination, and a prima case of obviousness has not been established.

In summary, the proposed combination does not yield the claimed invention, and even if it did there is no objective motivation articulated for making the proposed combination.

### *Claim 7*

Claim 7 calls for the tracer to have a polarity or charge that interacts with the bibulous substrate to retard migration of the tracer relative to migration of the analyte. The Office action rejected this claim in view of Boehringer et al combined with Leuversing because Leuversing discloses (at column 3) that antibody labeling particles can carry a charge. The apparent alleged

motivation for this combination was that Leuvering says the labels provide methods of detection that “are more sensitive than known techniques.”

There is no disclosure whatsoever in either Boehringer or Leuvering about the claimed interaction between a bibulous substrate and a tracer that has a polarity or charge, hence no prima facie case of obviousness has been established with respect to this claim. In addition, the alleged motivation for combining the references (a more sensitive labeled antibody) is not supported by the text of Leuvering. The discussion of a charge on the particle is disclosed at column 3, lines 51-58, in the context of a method of preparing the metal sol particles while avoiding flocculation of the particles. This is not an issue that is remotely related to the invention of claim 7 in which a polarity or charge is selected that interacts with a bibulous substrate to retard migration of the tracer. Since the claimed invention does not concern a method of preparing metal sol particles while avoiding flocculation, the cited references do not provide any credible motivation to make the proposed combination, and they therefore fail to establish a prima facie case of obviousness.

#### *Claims 8-10*

Claim 8 has been amended to state that the test strip contains in the mobilization zone at least one reagent that delays release of the tracer along the path of liquid flow relative to migration of the analyte along the path of liquid flow. Delayed-release tracers are discussed in applicant's specification at page 24, where it is noted that the tracer can be applied to the test strip in the presence of a delayed release molecule; page 16, lines 11-13 state that the tracer is in the mobilization zone. Claim 8 has also been amended to clarify that the delayed release reagent delays release of the tracer along the path of liquid flow relative to migration of the analyte along the path of liquid flow. Claim 8 depends from claim 1, wherein the path of liquid flow is from the sample application area, through the mobilization zone to the primary and secondary capture areas.

Claim 8 had been rejected as obvious over Boehringer et al. in view of Terminiello et al., which was said to disclose the treatment of membranes used in the analysis of a fluid sample with PVP to reduce void space in the membrane and promote absorption of the fluid fraction of a biological sample. The Office action alleged that it would have been obvious to treat the modified device of Boehringer et al. with PVP because such conditioning of the membrane provides an advantage by reducing void space and promoting absorption of the fluid fraction.

In contrast, what Terminiello et al. actually shows is an elongated test membrane 2 that has opposing planar faces. The membrane has a density gradient from one planar surface to another (column 11, lines 31-34), and the membrane is treated by applying a conditioning agent (such as PVP)(column 13, lines 1-4) exclusively from the relatively porous face (column 19, lines 41-44). Thus a liquid sample can be applied to one face of the membrane so that the liquid moves from one face to the other where a detection reaction occurs. This arrangement is said to be “essential” to isolate the component to be analyzed (such as serum) from other components (such as erythrocytes) that can interfere with the detection reaction. See column 11, lines 17-30 and the objects of the invention at column 9, lines 56-68.

A prima facie case of obviousness has not been established with respect to claim 8 because the proposed combination of Boehringer et al. and Terminiello et al. would not produce the claimed invention. If the references were combined as proposed by the Office action, the Boehringer test strip would have PVP applied along an entire face of the test strip, which would only inhibit migration of a fluid from one face of the test strip to the other face. Such an arrangement would have no effect on selectively delaying release of the tracer along the path of liquid flow relative to migration of the analyte. The path of liquid flow in claim 8 is from the sample application area, through the mobilization zone to the capture areas, which is *transverse* to the direction of flow affected by the Terminiello et al. membrane from one flat face of the membrane to the other. Since the PVP in Terminiello would only affect migration from one face of the membrane to the other, it would not affect differential flow of the tracer and analyte along the claimed path of liquid flow in claim 8.

In addition, Terminiello et al. provides no motivation to modify Boehringer et al. The Office action says that one skilled in the art would want to combine the references to promote absorption of the fluid fraction of the biological sample. However there is nothing whatsoever in Boehringer et al. to suggest that reference was concerned with that problem. This was not a problem with which that reference was confronted, so it can not be said to be a reason for combining the references.

Claim 9 recites specific reagents that are useful to delay release of the tracer along the path of liquid flow relative to the analyte. Claim 10 adds particular ranges of reagents, as supported at page 24, lines 30-31.

### *New Claim 75*

New claim 75 combines some of the features discussed in the foregoing claims, such as a bibulous substrate and a delayed release of tracer from the bibulous substrate so that the analyte migrates in advance of the detectable tracer and subsequent binding of tracer to first immobilized binding partner is inhibited and unbound tracer continues along the path of flow distally to the second capture area. As already noted, Boehringer et al. does not disclose or suggest a detectable tracer in a bibulous substrate; the only disclosure in the cited reference is of a tracer in a non-bibulous pad that is designed to promote flow of the analyte and tracer together without separation from each other. In addition, the test strip of claim 75 provides the advantages demonstrated in the Second Declaration of Buck in which slowed release of the tracer from a bibulous substrate provides enhanced binding efficiency in the primary capture area, and a higher ratio of tracer bound in the secondary capture area when analyte is present in the liquid sample.

As already noted, none of the cited references disclose or suggest a delayed release detectable tracer comprising an analyte or analyte analog. Although Terminiello discloses coating one face of a test membrane with PVP to exclude cells from one face of the test membrane, that coating would not delay release of the detectable tracer relative to movement of the analyte along the path of liquid flow from the sample application area to the capture zones. If it affected anything, it would equally affect migration of both the analyte and tracer from one face of the strip to another, which is transverse to the claimed direction of flow in claim 75.

### *Obviousness Type Double Patenting*

Some of the pending claims have been rejected under the doctrine of obviousness type double patenting. Applicant will file an appropriate terminal disclaimer once allowable claims have been identified.

### *Conclusion*

The cited references do not establish a prima facie case of obviousness with respect to the pending claims. The references, either alone or in combination, fail to disclose the invention as claimed. There is no motivation to make the proposed combinations. The unexpectedly superior results achieved by delayed migration of the tracer through the bibulous substrate also rebut any allegation of obviousness with respect to the claimed invention.

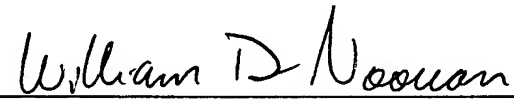
If any matters remain to be resolved before a Notice of Allowance is issued, the examiner is invited to telephone the undersigned.

Respectfully submitted,

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